PROGNOSTIC ANALYSIS OF PULMONARY METASTASECTOMY

Dissertation submitted to

THE TAMILNADU

Dr. MGR MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of degree of

MCh (BRANCH VII)

SURGICAL ONCOLOGY

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI – 600 020

FEBRUARY 2008

CERTIFICATE

I hereby certify that this is the bonafide work done by **Dr. DILEEP DAMODARAN** who is appearing for **MCh Surgical Oncology Branch VII** examination in February 2008, under my guidance in the College of Oncological Sciences, Cancer Institute (WIA), Adyar, Chennai.

Dr. HEMANTH RAJ MCh. PhD.

Professor and Chairman
Division of Surgical Oncology
Cancer Institute (WIA),
Adyar, Chennai.

ACKNOWLEDGMENTS

I am very grateful to all the patients, whom I have served and from whom I have learnt.

I am thankful to my teacher and guide in this project, **Dr.Hemanth Raj,** Professor and Chairman of Surgical Oncology. I am also thankful to **Dr.A.S.Ramakrishnan,** Associate Professor of Surgical Oncology for his inputs.

I am also thankful for the support given by the administration of the Cancer Institute (WIA), headed by the Director and Scientific Director **Dr.T.Rajkumar.** I have drawn inspiration from leaders in the realm of oncology in India, **Dr.Krishnamurthy,** Advisor and **Dr.Shanta,** Executive Chairman, Cancer Instutute (WIA).

The task would have been indeed more difficult without the help of the staff at the Tumor Registry and Epidemiology Division at the Cancer Institute (WIA).

CONTENTS

AIMS AND OBJECTIVES

1. To assess the long term results of pulmonary metastasectomy.
2. To assess prognostic factors which are likely to influence long term outcomes.
3. To find out a favourable subset of prognostic group who may benefit from pulmonary metastasectomy

PATIENTS AND METHODS

Between January 1997 to December 2006 , all patients who underwent pulmonary metastasectomy were included in this analysis. Individual patient data were obtained from the case records in the MMTR which also serves as a HBTR for Cancer Institute (WIA). A total of 53 patient records were obtained , of that only 42 cases were taken analysis. Patients who underwent planned sequential or staged metastasectomies were considered to have single metastasectomy and redo surgery.

Analysis was done using SPSS 11.0.1 statistical package. Following variables were tested : DFI ,unilateral or bilateral presentation, number of metastases, histological type and site of primary tumor, margin status, size of metastases, mediastinal nodes. Survival was calculated from the time of first metastasectomy to the last date of follow up by means of Kaplan – Meier estimate.

REVIEW OF LITERATURE

After the liver, the lung is the second most common site for metastatic involvement in neoplastic disease when all histologies are considered. Consequently, 20–54% of patients with cancer will have pulmonary metastases at some point in the natural history of their disease. In the absence of extrathoracic metastases (approximately 25% of patients with disseminated disease), complete resection is associated with increased survival, regardless of histology. With appropriate patient selection, life expectancy will often be improved with pulmonary metastasectomy. Cures are reported, either with resection alone or in combination with chemotherapy.[1] [2] Even in the context of unresectability, surgical forms of palliation may serve to improve quality of life. For other patients (e.g., nonseminomatous germ cell tumors) surgery may have a more diagnostic role such as defining residual disease potentially amenable to salvage forms of therapy.

HISTORY

The first, and perhaps most famous, planned pulmonary metastasectomy in the United States was performed in 1933 by Barney and Churchill for metastatic renal cell carcinoma[2]. During the nineteenth century there were sporadic reports of lung resections for metastatic tumors reported in the European literature. The first one of these reports was in 1855, by the French surgeon Sédillot, who removed a chest wall tumor and excised disease extending into the lung.

Almost 30 years later, in 1882, Weinlechner was credited for the first resection of a true pulmonary metastases.It was not for another 40 years that metastasectomy was performed as a separate procedure by Divis in Europe.[3] This was followed soon after by similar reports in the American literature by Torek and Tudor Edwards in the early twentieth century.[4]

These early reports, and others like them, paved the way toward general acceptance of pulmonary metastasectomy. In 1947 Alexander and Haight reported the first series of pulmonary metastasectomies.[5] By the 1950s there were numerous case series with similar accounts.

Today the indications for resection of secondary pulmonary malignancies have been broadened to include patients not only with recurrent disease, but those with multiple metastases, bilateral lesions, and essentially all histologies.

PATHOPHYSIOLOGY OF METASTASIS TO LUNG

Tumour spread is a complex process where the eventual outcome, in terms of secondary tumour development, depends on the result of a number of interactions between the disseminating tumour cell and the cells and tissues of the host. There are five major steps involved in metastasis, though it should be realized that the process, which is a dynamic one, passes from one step to another without interruption while a number of steps will be operating concurrently. Breaking the steps into a neat sequential series of events therefore gives a sense that there is more apparent order to the phenomenon than may actually be the case. Following tumour initiation and growth of the primary tumour mass (dealt with elsewhere in this volume) there must be:- (1) invasion and infiltration of cancer cells into surrounding normal host tissue with penetration of small vascular channels or lymphatics; (2) release of tumour cells, either as individual cells or as small clumps, into the lumen

of the penetrated vessels; (3) survival of the tumour cells in the circulation; (4) arrest of the surviving cancer cells in the capillary beds of distant organs; and (5) extravasation (or movement out of the lumen of the arresting lymphatic or blood vessel), followed by growth, of the disseminating tumour cells at the distant site .If all these steps are completed the result will be the formation of a secondary tumour in a distant organ.[6,7,8]. Hematogenous dissemination through the pulmonary arteries, and much less commonly through the bronchial arteries or lymphatics, is the most common form of spread for secondary pulmonary malignancies. This is thought to be the result of the lung's role as the primary capillary filter for the drainage of most organs. Lymphatic spread in pulmonary metastases is unusual and more commonly represents hematogenous dissemination with extension to the lymphatics. Direct tracheobronchial dissemination is also rare and accounts for only 2–5% of pulmonary metastases, most commonly associated with renal cell and breast carcinomas. Mediastinal involvement is also unusual and is frequently associated with concomitant parenchymal spread.

Do Metastases Metastasize?

In 1975, Hoover and Ketcham demonstrated, experimentally, that metastases do have the ability to metastasize. In their experiment, mice had their primary tumor amputated after pulmonary metastasis developed. These mice were then placed into parabiosis with normal syngeneic partners. Metastases were demonstrated in the non-tumor-bearing partners. In addition, both autopsy and other experimental data have defined the concept of metastases from metastatic disease. It is still poorly understood, however, when and how metastases are able to metastasize and more importantly how this process can be prevented from happening. It is thought that metastases need to follow the same steps as the primary tumor to metastasize: angiogenesis, intravasation, arrest, and extravasation.

Does Lung Cancer Metastasize to Lung?

Lung cancer is able to metastasize via lymphatic channels to the ipsilateral lung and, as suggested by some autopsy series, less commonly to the contralateral lung. These are patients with one primary lung cancer and intrapulmonary metastases. According to the 1997 lung cancer

staging revision of the American Joint Commission of Cancer and the Union Internationale Contre Cancer, these patients are considered to have M1 disease. It is difficult, however, to determine if these patients have synchronous lesions or a primary lung cancer with intrapulmonary metastases. Ichinose et al have used DNA flow cytometry to evaluate these lesions. With this technique, lesions are determined to be synchronous if they demonstrate completely different DNA ploidy. If both tumors show diploidy or when at least one DNA index of abnormal clones between two aneuploidy tumors

SYMPTOMS AND PRESENTATION

Approximately 75–90% of patients with secondary pulmonary malignancies are asymptomatic and, therefore, their disease is most commonly discovered incidentally on routine or follow-up radiological examinations.[8] Symptoms, when they do occur, typically result from a delayed diagnosis with endobronchial or pleural involvement, large bulky disease, or central tumors. Patients may present with cough and hemoptysis suggesting an endobronchial lesion and thus warranting bronchoscopic examination. Endobronchial metastatic lesions are extremely rare, less than 2%, in patients who die of solid tumors with

breast, kidney, pancreas, colon, and melanoma as the most common sources.Another presenting symptom may be dyspnea, which is usually secondary to airway obstruction, a pleural effusion, parenchymal replacement by multiple metastatic lesions, or lymphatic spread. Finally, chest pain, wheezing, or pneumothorax may be other modes of presentation.

RADIOGRAPHIC APPEARANCE

Every patient with a history of cancer should be routinely followed up and depending on the primary tumor with a plain CXR and/or a computerized assisted tomography (CT) of the chest. The presence of a new solitary pulmonary nodule in a patient with a prior malignancy essentially confirms the diagnosis of cancer. In one study in which 800 extrathoracic cancer patients presented with a new solitary pulmonary nodule, 87% were found to have a malignancy (63% primary lung cancer, 24% metastatic disease).[9] The likelihood of finding metastases in a cohort of patients, all with no known cancer, therefore, is even lower. In one such study only 3% of solitary pulmonary lesions in 887 such patients were metastatic.[10].

Once a nodule has been found on a CXR, in a patient with a history of previous extrathoracic cancer, a diagnostic dilemma exists in determining whether the lesion represents metastatic or primary disease. This distinction has significant implications with respect to treatment and prognosis.The likelihood that a given pulmonary nodule is metastatic is dependent on the histology of the primary tumor .[9].

Metastatic lung nodules themselves are most commonly described as being well circumscribed with smooth margins and spherical shape as well as located in the periphery of the lung[11] . In addition, there is a predilection for a more basilar distribution consistent with this region's increased blood flow in the upright position.Irregular borders and associated linear densities are more frequently associated with primary bronchogenic lung cancer.[11]

Primary malignancies most commonly metastatic to the lung are carcinomas of breast colon kidney uterus prostate and oropharynx. Tumors with the highest predilection for pulmonary metastases are choriocarcinoma osteosarcoma testicular tumors melanoma Ewing's sarcoma and Kaposi's sarcoma.

Approximately, 70–80% of tumor nodules less than 6 mm will be detectable by CT of the chest. In addition, CT scan may further define the number and location of the nodules, aiding in assessment of resectability. However, modern high-resolution CT scan techniques are able to detect lesions in the 2–3 mm range that are often difficult to be palpated during thoracotomy.

In addition to CXR and CT scan, other imaging modalities such as magnetic resonance imaging (MRI) may also be of use when assessing resectability and attempting to visualize potential involvement of the spine or surrounding structures.[12] The resolution of this study, however, is still inferior to CT. Positron emission tomography (PET) scans may have a role in characterizing metastatic pulmonary nodules, for breast carcinoma, colorectal tumors, and cholangiocarcinomas. Spiral CT has been shown to be superior to PET scans in diagnosing metastases from primary bone tumors (i.e., osteosarcomas and Ewing sarcomas)[13]. Occasionally, nuclear radiological techniques are useful in determining lung metastases from thyroid tumors as well as other neuroendocrine tumors.

CRITERIA FOR SURGICAL RESECTION

In chemo-sensitive tumors clinical experience has allowed identification of criteria by which to select patients for surgical resection. Most important of this is how effective chemotherapy is for a particular type of cancer. A secondary factor is whether the natural history of that cancer is to metastasize predominantly to lungs or to disseminate widely. Two types of cancer which illustrate the development of improvements in chemotherapy are breast cancer and germ cell cancer.

Most solid tumors that metastasize to the lung are insensitive to currently available chemotherapy. Pulmonary resection is an important primary form of treatment for these malignancies , which include colorectal ,some gynaecological cancers, head and neck cancers, malignant melanoma and osteogenic and soft tissue sarcomas.

Consistently important criteria include the following – (1) control of the primary tumor or ability to resect primary tumor completely simultaneously with resection of metastases,(2) ability to resect metastatic disease completely;(3) absence of extrathoracic metastases ;(4)ability of the patient to withstand the procedure ; and (5) absence of better alternative systemic treatment.the criteria found to be important in

select series are DFI, tumor doubling time , number of pulmonary metastases. The criteria for surgical resection will evolve with better understanding of tumor biology, with better systemic treatment. Majority of the patients relapse and require systemic treatment.

TECHNIQUE OF PULMONARY RESECTION

The ojective is to remove all gross tumor while preserving as much as normal parenchyma as possible. Most of them are small , discrete , sub pleural nodules that can be easily removed by wedge resection using GIA or TA stapler. If not accessible by stapler , it can be excised by needle tip electrocautery. Usually the preferred margins are 0.5 to 1.5 cm of normal lung all around. Laser can also be used to accomplish wedge resections, but it carries no advantage over needle tip electrocautery. Argon plasma coagulator may be helpful in obtaining haemostasis .

For larger lesions or centrally located lesions may require lobectomy or pneumonectomy procedures for their complete removal , but such resections donot increase the chance of cure after metastasectomy. They may offer long time survival and hence such extensive procedures should be considered carefully as these patients may develop subsequent lesions in the remaining lung.

Approaches to metastasectomy may be either a thoracotomy , or median sternotomy or clam shell thoractomy for bilateral lesions. Minimally invasive procedures like video assisted thoracoscopic surgery ,VATS has also been advocated . but the procedure lacks the tactile sensation , and its imperative that the surgeon systematically inspect and palpate the entire lung to ensure complete removal of all tumor. Therefore most thoracic oncologists limit VATS to diagnosis and staging of pulmonary metastases.

Role of lymph node dissection in the management of pulmonary metastases has not been defined. Lymph node involvement is occasionally seen and may be associated with poorer long term survival, but the implications in patient management are unclear. Systematic lymph nnode dissection is not recommended, only suspicious nodes be resected in the interests of proper diagnosis and for resecting all gross disease.

	Lateral Thoracotomy	**Median Sternotomy**	**Clamshell**	**VATS**
Advantages	Familiar approach; optimum exposure to hemithorax	One operation accesses and treats bilateral disease; good exposure to anterior mediastinum	Good exposure to hemithoraces and to entire mediastinum	Low morbidity; good exposure to lung surface and pleural space
Disadvantages	Bilateral disease requires 2 procedures	Limited exposure to left lower lobe	Higher morbidity; longer operating time	Lesions below lung surface difficult to locate; no palpation of lung
Relative patient discomfort	+++	++	++++	+
Special considerations	A lung without evidence of disease on imaging will not be explored	Use with caution in patients who may not tolerate traction on the heart	Problem with malunion of sternum	Reserve for patients with minimal, easily accessible disease and long DFI

RESULTS OF PULMONARY METASTASECTOMY

Pulmonary metastasectomy in appropriately selected patients has been shown to improve survival. When all histologies are considered, the 5-year survival rates for patients undergoing resection of secondary pulmonary malignancy are 25–35%. In an attempt to more clearly define those patients most likely to benefit from metastasectomy, many series have evaluated potential prognostic indicators. For example, short tumor doubling time is frequently a sign of an aggressive lesion. It has been proposed that patients with such tumors, therefore, might not derive a survival benefit from resection. Reports of such studies, however, are equivocal. Moreover, the practical application of such a measurement is difficult. Disease-free interval has also been studied in an attempt to predict outcomes. Longer disease-free intervals, however, have not been consistently associated with a better prognosis. An increased number of nodules seen on preoperative testing might intuitively be associated with a poor prognosis. In general, patients with multiple nodules do more poorly then those with a solitary nodule. Again, however, there is great variability.

Histology 5-year survival without metastasectomy 5-year survival with metastasectomy

All histologies25–40%

Breast cancer - 35–50%

Colorectal cancer - 40–45%

Germ cell tumors 68%

Head and neck squamous cell carcinoma 29–60%

Melanoma - 21–36%

Osteosarcoma - 20–40%

Renal cell carcinoma - 13–54%

Soft tissue sarcomas - 20–40%

Urinary tract cancer - 25–43%

The number of nodules above which resection is unwarranted is also unclear. As many as 20–30 metastasectomies can be performed at one operation with good results. In addition, the number of nodules estimated with preoperative testing is often inaccurate. As such, multiplicity may be more appropriately used to assist in the assessment of tumor resectability. None of these criteria for predicting positive outcome from metastasectomy has been universally established. Most

studies have proposed that complete resectability is the only universal determinant of prognosis across all histologies.

Many of the aforementioned studies attempting to evaluate prognostic determinants in pulmonary metastasectomy have been faulted for insufficient statistical power. One group, however, reported 5206 cases of pulmonary metastases from various sites from the 18 medical centers of the International Registry of Lung Metastases. In this retrospective review, three parameters were shown to have prognostic significance regardless of primary histology: resectability, a disease-free interval of over 36 months, and solitary versus multiple metastasis. As a result, they have proposed a four-group staging system based on the number of poor prognostic indicators present in a given . Although staging systems such as this one may better define those patients most likely to benefit from metastasectomy, survival in patients following surgery, even with poor prognostic indicators, is superior to any other treatment. Consequently, some feel that metastasectomy should be offered to appropriate patients regardless of these factors, with the possible exception of inability to perform complete resection.

In addition to the aforementioned factors equivocally associated with prognosis, other factors have been clearly shown not to affect outcome. These factors include unilateral versus bilateral disease, age, gender, and wedge resection versus formal lobectomy.

Recurrence is the most common cause of death following complete pulmonary resection of metastatic disease. Despite this, repeat resections have contributed to prolonged survival for a number of histologies. The most studied of these is soft tissue sarcomas. In a study by the National Cancer Institute in which patients underwent reresection for softtissue sarcomas, no difference in the actuarial 5-year survival was found in those undergoing one, two, and even three resections for recurrence. Preoperative selection criteria similar to those utilized with the initial resection are important in appropriately choosing patients for repeat resection. This ensures the absence of disseminated disease and the ability of a given patient to tolerate the proposed procedure. Once screened, therefore,resection of recurrent disease will be offered to the majority of patients (approximately 70%) should no extrathoracic dissemination be present and should the lesion be amenable to resection.

METASTASES TO THE LUNG

Osteosarcoma

Like soft tissue sarcomas, osteosarcoma has a strong predilection for metastasis to the lung. In addition, the lesions themselves are frequently multiple and often recur despite resection. Consequently pulmonary involvement is responsible for the majority of deaths in patients with this disease. Approximately 10–20% of patients will have distant metastases on initial evaluation, and, as with other histologies, CT of the chest is the imaging modality of choice for detection.

Prior to the introduction of chemotherapy, the overall survival from osteogenic sarcoma was only 10–20%.[14] In the early 1970s, however, the use of chemotherapy, especially high-dose methotrexate, substantially improved outcomes.[15] Later, with the introduction of multimodality therapy, chemotherapy (doxorubicin, high-dose cyclophosphamide, and cisplatin) combined with resection, improved 5-year survival rates to 32–40%. [16]

Most studies conclude that complete surgical resection is associated with increased survival. [18]

Soft Tissue Sarcoma

Most soft tissue sarcomas metastasize within the first 2 years of diagnosis, with the lungs being the most common site (80–90% of the time). Consequently, secondary pulmonary disease is the primary cause of death in these patients. The predilection for dissemination to the lungs also emphasizes the importance of pulmonary surveillance in following up sarcoma patients.

Of those with soft tissue sarcomas, however, 20% will have isolated disease and are candidates for resection. Unlike pulmonary metastases from melanoma and carcinoma that are commonly solitary, sarcomatous involvement of the lung tends to be multiple. Five-year survival rates following resection of secondary pulmonary disease are 20–30%, a significant improvement over those patients who are not resected.[19]

A large retrospective study from Memorial Sloan-Kettering reviewed 3149 patients with soft tissue sarcomas. Of these patients, 719 developed pulmonary metastases, and 248 underwent at least one pulmonary resection. Three independent negative prognostic factors

were identified: three or more lesions, largest metastases' diameter more than 2 cm, and high-grade primary tumor histology.[20] A much smaller study, including 23 patients, found similar prognostic factors associated with poor outcomes. These included three or more lesions and disease-free interval of less than 6 months

Colorectal Carcinoma

The incidence of colorectal carcinoma in the United States is high, with approximately 100,000 new cases occurring each year. Approximately, 10–30% of these patients will go on to have metastases. Because of this high incidence of recurrence it is important to follow up these patients very closely. The most common extraabdominal location of secondary disease is metastasis to the lung. Unfortunately, such pulmonary involvement is also frequently associated with disseminated disease, usually involving the liver. Ten percent of colorectal cancer patients with metastatic involvement of the lung, or 1–3% of those with colorectal cancer, will have isolated pulmonary disease [21,22]. These patients benefit from resection. [21] Five-year survival rates following resection of colorectal metastases to the lung are 20–40% and 10-year survival is 20%.[21]. In several series examining this issue, the 5-year

survival rates following dual metastasectomy have been reported to range from 21 to 52%.In addition, patients who develop a pulmonary recurrence after a hepatic resection for colorectal metastases appear to benefit from pulmonary metastasectomy. [23] The only positive prognostic factors that are consistent among four recent series of patients after pulmonary metastasectomy for colorectal metastases are complete resection and a normal CEA level prior to thoracotomy.[24]

Breast Carcinoma

Breast cancer accounts for 30,000 deaths each year and is currently the second most common cause of cancer deaths in females in the United States, behind lung cancer. Pulmonary involvement in breast cancer is most commonly associated with widespread disease, thereby contraindicating resection in the majority of patients. A thorough preoperative workup, specifically searching for extrapulmonary disease, is necessary in considering patients for pulmonary resection. When properly screened, up to 20% of patients will be found to have isolated pulmonary disease and may potentially benefit from metastasectomy.

Considering that a pulmonary nodule in a patient with known breast carcinoma is more likely to be primary lung cancer,[25] histological diagnosis is needed to proceed with appropriate management. A diagnosis of adenocarcinoma on biopsy obtained by FNA or wedge resection, however,requires the use of further assays (e.g., ER/PR receptor status and cytokeratin stains) to establish a diagnosis of breast cancer. [26]

Five-year survival rates after metastatic resection range from 35% to 62%. [27] Despite these results, high-dose multidrug chemotherapy and bone marrow rescue are the primary forms of treatment currently offered to patients with disseminated pulmonary involvement. Patients with ER-receptor-positive metastases and/or complete resection appear to have a more favorable prognosis.

Germ Cell Tumors

Germ cell tumors account for only 1% of all cancers, but are the most common malignancy in males between 15 and 35 years of age. The most common site of distant metastasis for these tumors is the lung. Overall, greater then 90% of germ cell tumors will be cured with

cisplatin-based chemotherapy and, therefore, the primary treatment is nonsurgical. Of those patients with nonseminomatous germ cell tumors with pulmonary metastases, 70% will have normalization of tumor markers and radiolographic clearance of disease, a complete response, following chemotherapy. Patients with residual radiographic evidence of pulmonary involvement, despite normal serum markers (AFP, hCG-) after chemotherapy, are frequently referred for resection to determine if viable tumor exists in these partial responders and nonresponders. Of those who do not respond to initial chemotherapy, 25% will respond to salvage forms of treatment. In addition, patients with radiological evidence of disease and abnormal serum markers may also be candidates for surgical salvage if their disease is considered resectable. Because no reliable method of preoperative diagnosis exists, and the potential for malignant and chemoresistant degeneration of benign teratomas may occur, resection of any residual disease is indicated. [28]

Controversy exists surrounding the appropriate management of residual pulmonary masses found in seminoma patients following chemotherapy. Less then 25% of such residual disease will represent viable tumor and less than 5% will reveal teratoma. For this reason, and

the morbidity associated with resection, expectant management is advocated by some. For patients with larger masses, radiation therapy, as the only treatment or preceded by resection, may be indicated.[28]

Melanoma

Melanoma is responsible for 1–2% of cancer deaths. The lung is involved in secondary disease 15% of the time. [29] Although the lungs are one of the most common sites of distant spread, only 5% of patients with such involvement have an absence of extrathoracic involvement. More commonly, lesions found on CXR are a manifestation of widespread disease at the time of diagnosis and such patients are traditionally treated with chemotherapy. A thorough search for dissemination is indicated in melanoma patients being considered for resection. Although melanoma does have the lowest 5-year survival rate following metastasectomy,[30] long-term survival benefits have been reported in many cases. Thus, the surgeon may wish to apply more rigorous criteria in selecting patients with melanoma for pulmonary metastasectomy.[31]

Leo et al reviewed 328 patients identified in the international registry of lung metastases who underwent resection of melanotic pulmonary metastases.[32] Of these patients, 282 underwent complete resection. Independent unfavorable prognostic factors included multiple metastases and time to pulmonary metastases of less than 36 months.

Head and Neck Squamous Cell Carcinoma

Forty percent of patients with head and neck squamous cell carcinoma will go on to develop distant disease. In these patients the lung is the most commonly affected organ. Some of the same risk factors that predispose patients to head and neck cancer also put patients at risk for primary cancer of the lung. As a result, a solitary nodule found in follow-up is more likely to be primary lung cancer. For this reason, these lesions should be treated as such until proven otherwise. Five-year survival rates following metastatic resection range from 29 to 60%.[33] Positive prognostic factors include single lesion, disease-free interval of more than 2 years, locoregional control, and complete resection. [33]

Urological Tumors

Of approximately 30,000 patients diagnosed with renal cell carcinoma each year, 60–70% will go on to develop metastases. The most common metastatic site is the lung. Unresected, less than 5% of patients will survive 5 years. In contrast, after complete pulmonary metastasectomy 5-year survivals range between 37 and 54%. [34] Positive prognostic factors include complete resection, disease-free interval of more than 2 years, and fewer than seven lesions. In view of these results, and the fact that renal cell carcinomas are chemoresistant and radioresistant, surgical resection of pulmonary metastases is indicated for most cases.[35]

Of patients with transitional cell carcinoma 50% will also develop pulmonary metastases. Although reports in the literature are sparse, isolated disease, when completely resected, may result in 5-year survival rates of approximately 25%.

Endocrine Tumors

Pulmonary metastases from these tumors are rare. Occasionally resection may be indicated to alleviate symptoms of hormone

production.A review of 25 patients who underwent pulmonary metastasectomy for different types of endocrine tumors showed a 61% 5-year survival.Independent predictors of poor survival included positive mediastinal lymph nodes, incomplete resection, and short disease-free interval.[36]

Gynecological Tumors

Uterine and cervical cancers have also been shown to respond to metastasectomy in appropriate candidates. A 24–52% 5-year survival following pulmonary metastasectomy has been reported.[37] For choriocarcinoma multidrug chemotherapy is the primary form of treatment.Resistant lesions should be considered for resection. Five-year survival rates approaching 50% have been reported.[38]

ALTERNATIVE FORMS OF THERAPY IN SECONDARY PULMONARY DISEASE

Isolated Lung Perfusion

Systemic toxicity of chemotherapeutic agents frequently limits the dose that would otherwise eradicate micrometastatic disease in the lung.

Isolated regional lung perfusion therapy is a novel form of delivery that has shown some promise. This technique is analogous to isolated limb perfusion, a therapy used in the treatment of advanced sarcoma and melanoma. The nearly closed nature of the pulmonary circulation, with only 5% being perfused by the bronchial circulation, makes the lung an ideal organ for isolated perfusion. Isolated lung perfusion has been applied to a number of histological types including colorectal carcinomas, sarcomas, melanoma, and renal cell carcinoma. Eight patients with unresectable pulmonary metastases from soft tissue sarcomas were enrolled in a Phase I trial that demonstrated that the technique was safe and feasible but none of the patients responded to the therapy.[39]

Lung transplantation

The ideal solution for treating patients with unresectable metastatic cancer to the lung is to entirely remove the diseased organ and replace it with healthy lung. The patient must not have tumor elsewhere, either at the primary tumor site or other metastatic sites. Although this can never be determined with certainty, a long disease-free interval at all sites except the lung and a thorough metastatic workup are encouraging.

In this context the indication for lung transplantation would be oncologic rather than respiratory. Thus, it would be potentially curative treatment for localized disease, not replacement of a failed organ.

Solid-organ transplantation for cancer therapy is a proven concept. In patients with hepatocellular carcinoma who have either one tumor mass less than 5 cm in diameter or up to three nodules smaller than 3 cm, the survival at 5 years after liver transplantation is 70% and the recurrence rate is approximately 15%.[46] The experience with lung transplantation for cancer is small and not nearly so promising. de Perrot et al. summarized the world experience with transplantation for bronchioloalveolar carcinoma. Of 26 reported transplants, 13 have recurred, 11 of which were in the transplanted lung.[46]

Radiofrequency Ablation

Radiofrequency ablation (RFA) delivers thermal energy through a catheter delivery system resulting in coagulation necrosis. This technique may be used in the management of metastatic disease to the lungs. Further studies investigating the role of this technique are needed.

Palliative Therapy

Palliative therapy should be considered for symptomatic patients whose disseminated disease or unresectability precludes curative forms of therapy. Endobronchial lesions are frequently symptomatic. Commonly they are associated with unresectable disease and frequently require palliative therapy. Those patients with endobronchial lesions who present with hemoptysis may respond well to a short course of external beam radiation.

Obstructive lesions may be treated bronchoscopically with mechanical debridement, laser ablation, brachytherapy, or stenting. Nd:YAG laser provides the best penetration, coagulation, and thermal necrosis and may be administered through a flexible fiberoptic system.

Photodynamic therapy

Photodynamic therapy (PDT) is a technique for killing cells that employs nontoxic compounds, photosensitizers, that tends to concentrate in tumor cells and can subsequently be activated with visible light. When the photosensitizer is exposed to the correct wavelength of light, it has

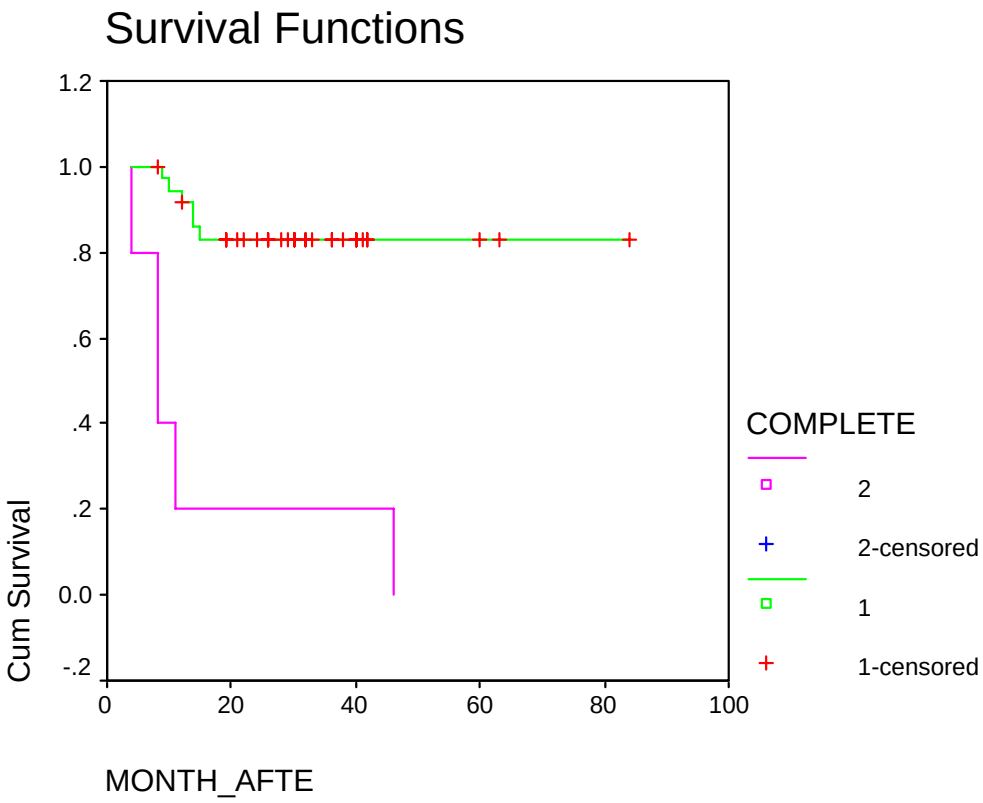
the ability to transfer energy to oxygen. It is the excited species of oxygen that eventually cause cell death. PDT is thought to work by both direct tumor cell kill as well as destruction of the tumor's neovascularization. PDT is currently approved for obstructing as well as early stage endobronchial lesions and, in select cases, may be a good option.

Other supportive measures

Malignant effusions secondary to neoplastic disease may be voluminous and consequently symptomatic. When they occur, they may be treated by VATS or bedside drainage followed by talc pleurodesis. Internal shunting or external drainage of a pleural effusion is an option for a failed pleurodesis or, occasionally, as the primary palliative procedure.

Pericardial effusions occurring in the setting of disseminated disease may become symptomatic. Percutaneous drainage, subxiphoid window, or VATS window procedures are the options for this condition.

COMPLETENESS OF RESECTION (R0 Vs R1)

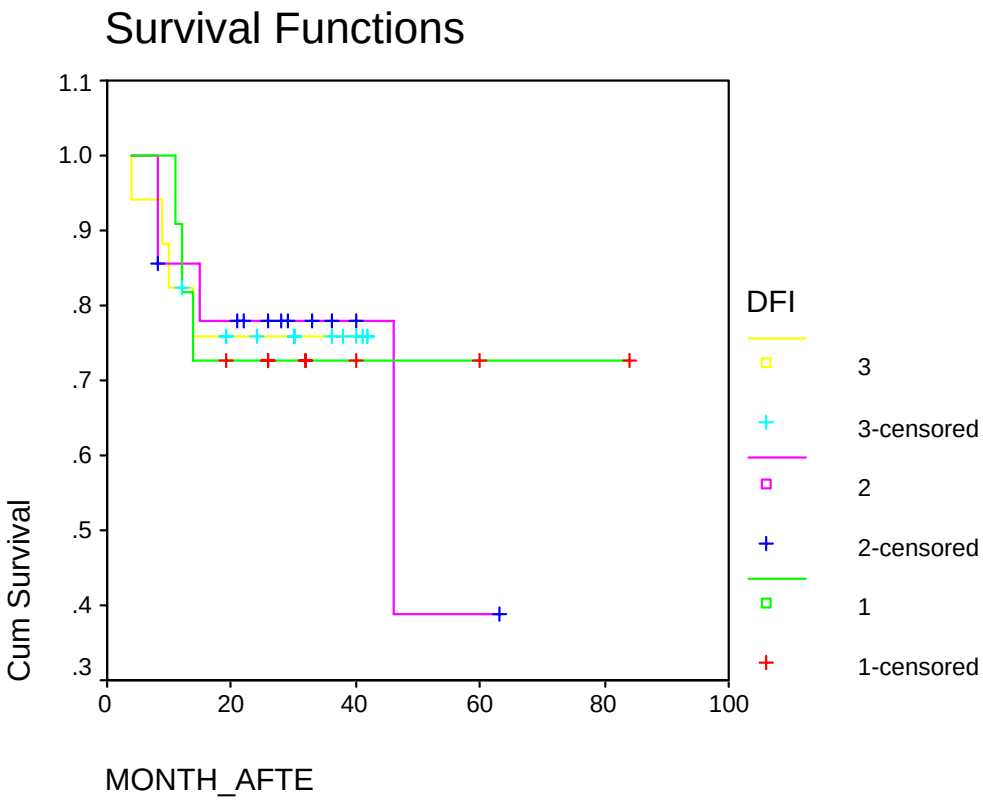


DISEASE FREE INTERVAL (DFI)

1- DFI 0 To 11 Months

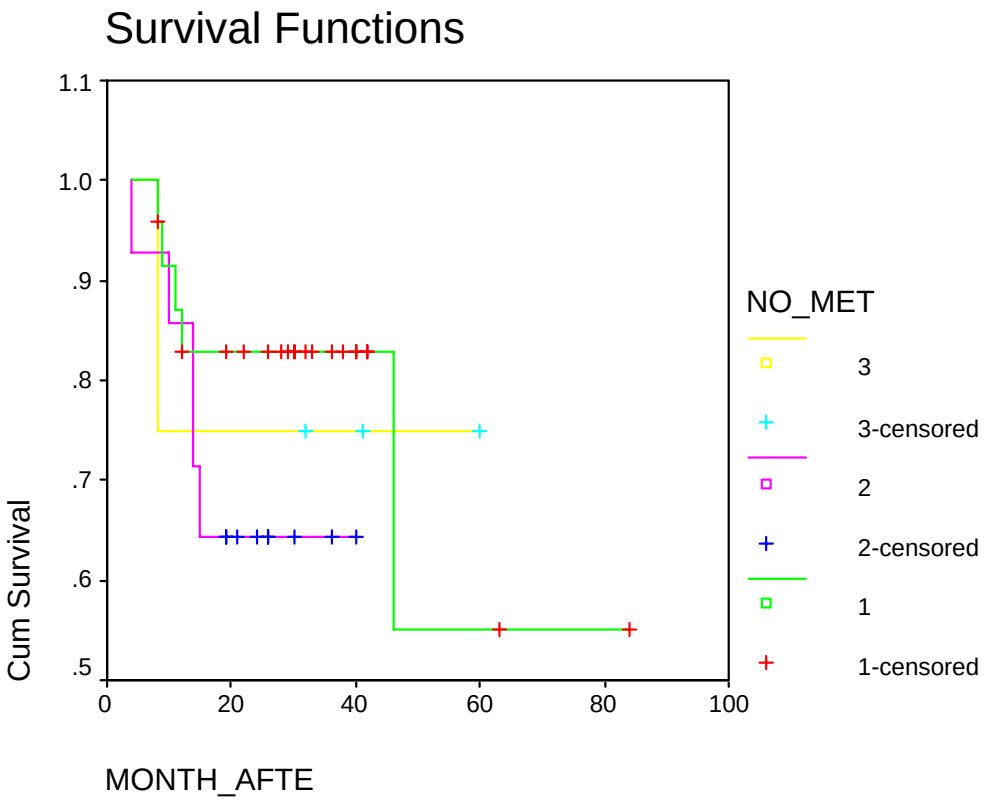
2- DFI 12 To 35 Months

3- DFI > 36 Months



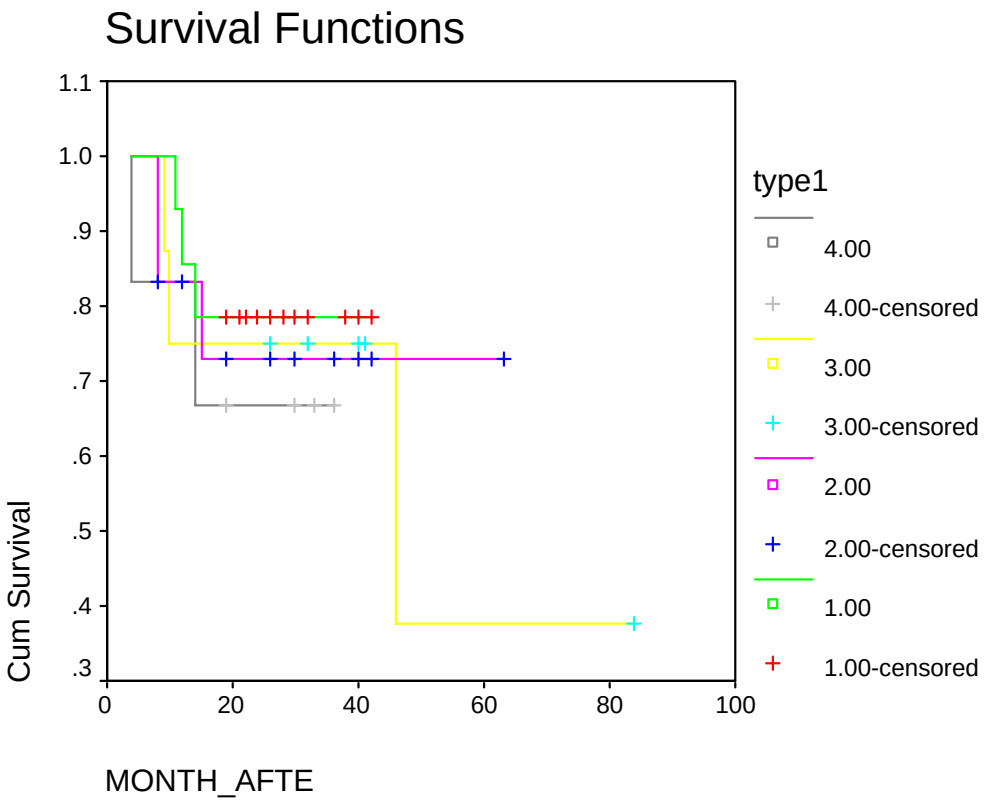
NUMBER OF METASTASES

1. 1 Single Mets
2. 2 To 3 Mets
3. > 4 Mets



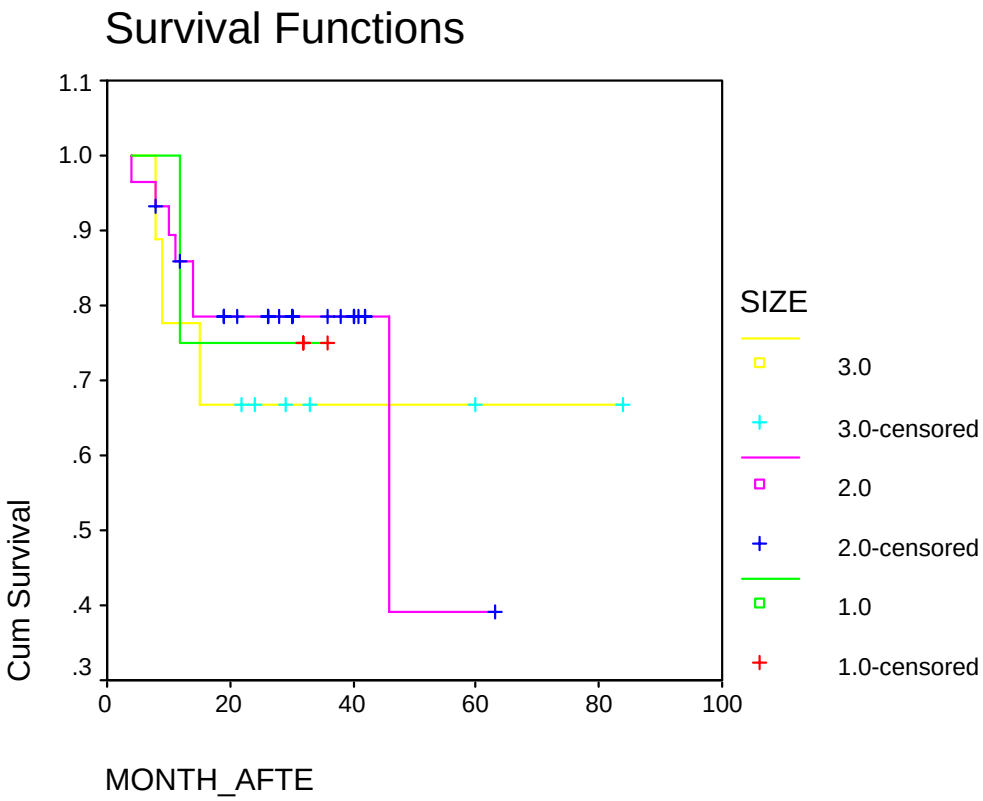
TYPE OF TUMOR

1. OSTEOSARCOMA
2. SOFT TISSUE SARCOMA
3. RECTUM
4. OTHER EPITHELIAL TUMORS



SIZE OF THE METASTASIS

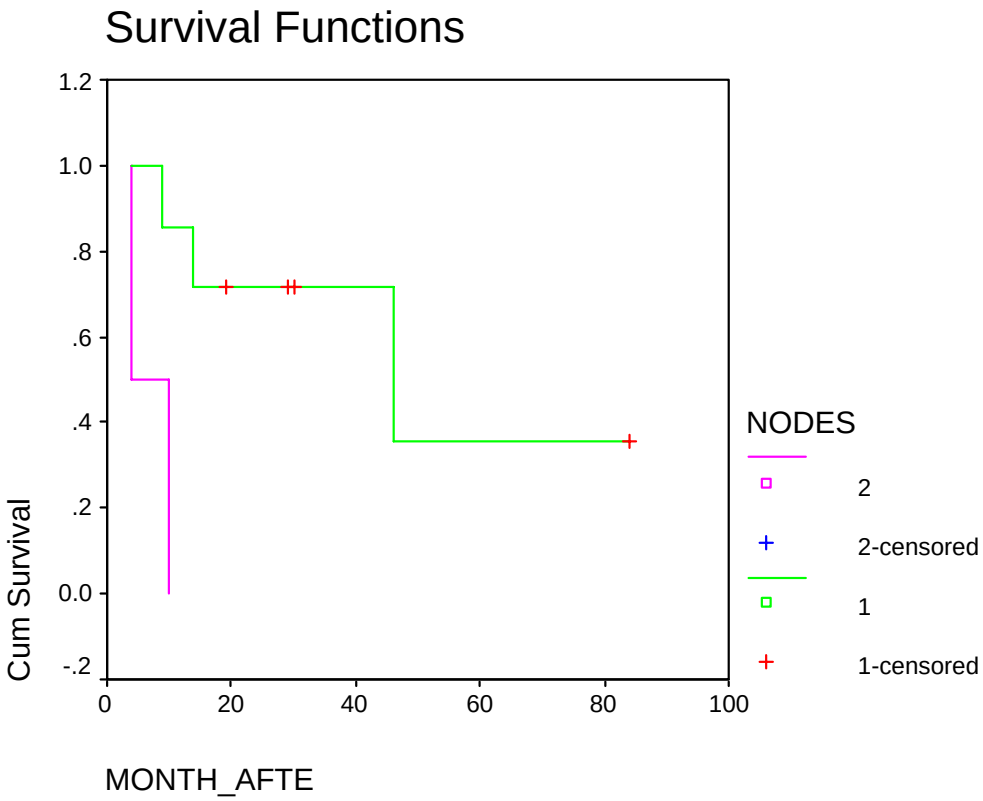
1. < 1 cm
2. 1.1 to 4 cm
3. > 4 cm



MEDIASTINAL NODES

1. Node negative

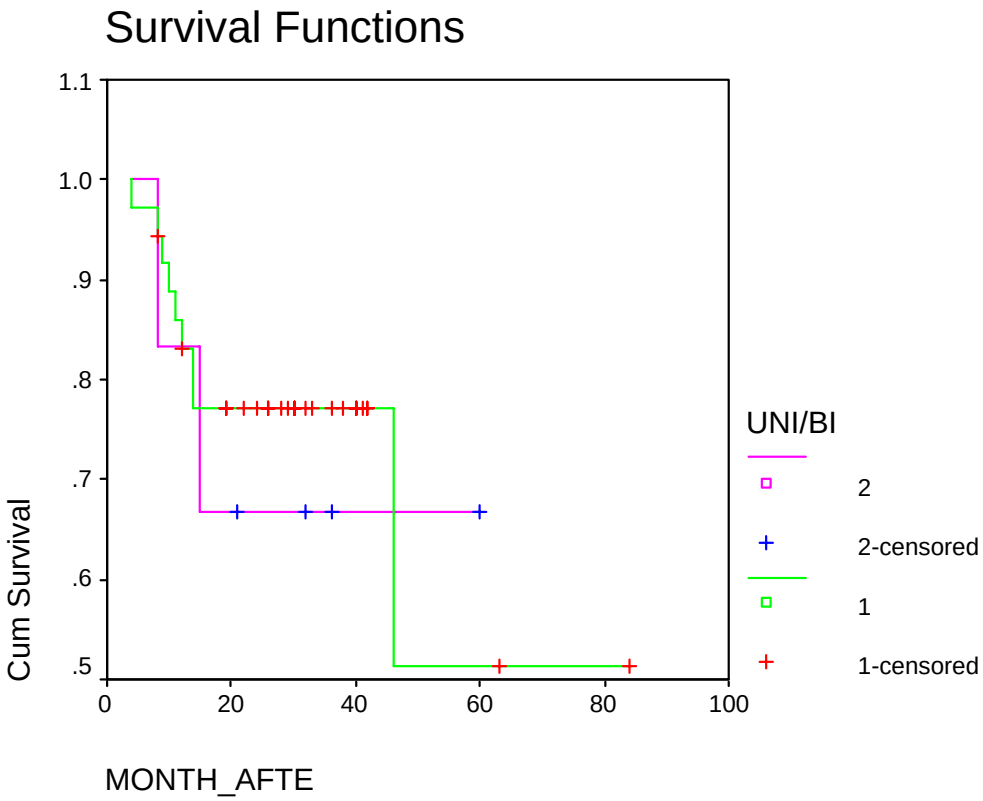
2. Node positive



UNILATERAL OR BILATERAL PRESENTATION

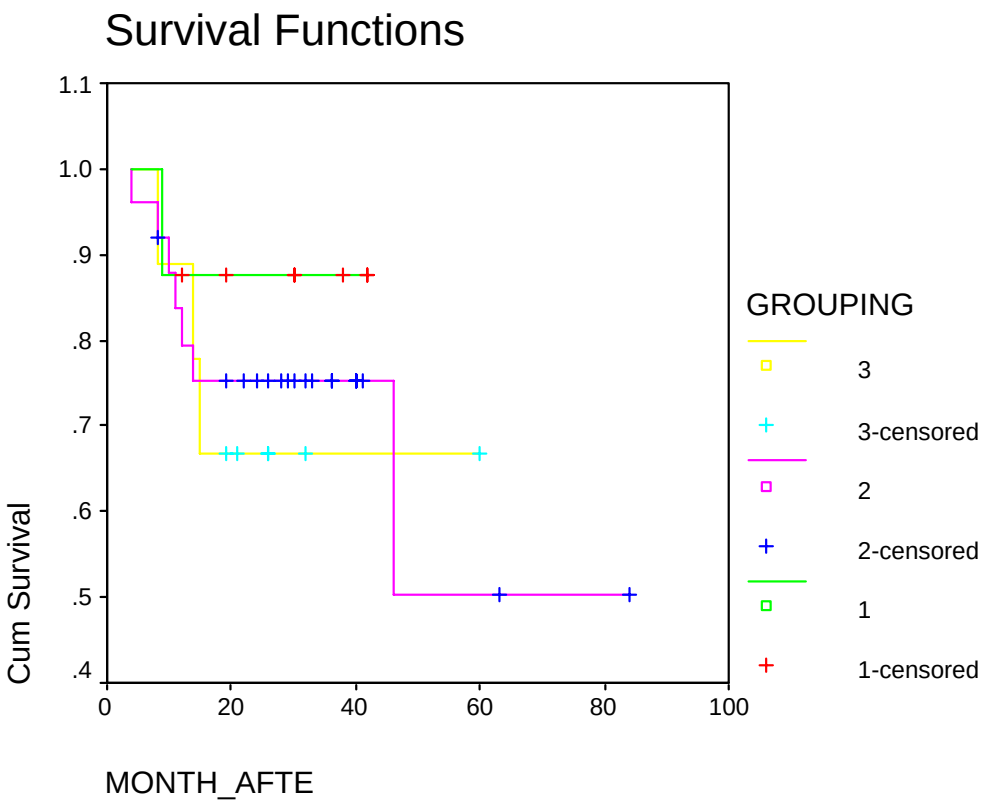
1- Unilateral

2- Bilateral



PROGNOSTIC GROUPING

1. Group I – Resectable, no risk factors (DFI > 36 months and 1 metastases)
2. Group II (DFI < 36 months or multiple metastases)
3. Group III (DFI <36 months and multiple metastases)



RESULTS

A total of 53 patients underwent pulmonary metastasectomy , of which only 42 patient records were taken for analysis. The rest 11 patients were excluded based on various reasons , benign pathology (5), different histology (3), unresectable disease (3). These 42 patients underwent 45 metastasectomies (3 for recurrent disease). Staged bilateral metastasectomy was considered as single procedure. Survival was calculated from the time of first metastasectomy to the last date of follow up. Average follow up was 28 months (range 4 months to 84 months).13 patients were lost to follow up after a variable period of follow up ranging from 19 months to 60 months (average – of 32 months).

Patient features

Overall there were 23 males (54.7%), and the mean age was 31 yrs (median 28 yrs , range 13 -64 yrs). Sarcomas , both soft tissue and osteogenic constituted 62 % of pulmonary metastasectomies (osteosarcoma – 33%, sarcoma – 29%), and the rest comprised of

epithelial tumors (33%, which includes various subsites like breast , parotid , cervix , endometrium, testis and rectum [14 %]) and other sites (2 patients 4%, Giant cel tumor of bone and choriocarcinoma). In the whole series the , 26% ofpatients had DFI of 0 to 11 months, 33% had DFI of 12 to 36 months and 41 % had DFI of > 36 months. The median DFI was 31.3 months. Most common presentation was unilateral (86%) . The surgical approach was monolateral thoracotomy in 86 % and bilateral staged thoracotomy in 14 %. For large majority of tumours wedge resections (71%) , were the procedure most commonly done, lobectomies (29 %) unilobar or bilobar were usually done for large lesions or centrally placed lesions not amenable to wedge resections.

On the basis of pathological analysis 57% of patients had only single metastases, 33% had 2 to 3 metastases and around 10% had > 4 metastases. The resections were complete (R0) in 88% and R1 in 12 %. The maximum numbers of metastases were 22 in one patient with NSGCT of testis.

Majority of the metastases were of size between 2 to 4 cm (69%),lesions less tha 1 cm and more than 4 cm accounted for 10% and 21 % respectively.

Lympnodal dissection was done in 9 cases of the total 12 lobectomies and metastases to these lymph nodes were found in only 2 cases.

6 patients reccured of which only two patients underwent redo metastasectomy.

Survival

There were no operative mortality in the entire cohort of patients. The overall survival irrespective of the type of primary in this study was 66% at 5 years.

The following variables were tested for assessing the impact on prognosis:

Completeness of resection (R0 Vs R1)

The overall survival was 82% at 36 months for patients with R0 resection. In patients who had R1 resection , none of them survived beyond 45 months , overall survival was only 20% at 36 months. This difference was not found to be significant in both univariate and multivariate analysis using Cox regression analysis.

Disease free interval (DFI)

For patients with a DFI of 0 to 11 months, the overall survival was 72% at 36 months. For patients who had DFI of 12 to 35 months the overall survival was 76 % at 36 months . Patients who had DFI > 36 months the overall survival was 76% at 36months. This was also tested tested for significance in both univariate and multivariate analysis using Cox regression analysis and was not found to be significant.

Number of proven metastases

Patients with single metastases had survival of 82.5% and 69% at 36 months and 60 months respectively. For the patients who had 2 to 3 metastases the survival was 61% at 36 months, and as no further events occurred beyond this, survival at 60 months could not be calculated. In patients who had > 4 metastases the survival was 75% at both 36 months . This variable also was not found to be significant in both univariate and multivariate analysis.

Histological type of tumor

The overall survival among patients with osteosarcoma was 76.7%at 36 months. In patients with metastatic soft tissue sarcoma was 72.3% at 36 months. The overall survival in patients with metastatic rectal tumors was 66.7% and 64.8% in patients with other epithelial carcinoma at 36 months respectively.

Mediastinal nodes

In patients who had positive mediastinal nodes none of them survived beyond 10 months. While in patients who where node negative 76% survived at 36 months and 40% at 60 months respectively.

Unilateral and bilateral metastases

The survival in patients who had unilateral metastases was 76.5% and 64.8% at 36 months and 60 months respectively, while patients who had bilateral metastases the survival was 65.6 % and 64.8% at 36 months and 60 months respectively this was also not found to be significant in univariate and multivariate analysis.

Size of the metastases

Survival among patients who had lesions less than 1 cm were 75% at 36 months, while larger lesions >4 cm and lesions 1 to 4 cm had survival of 65% and 70% respectively. However in both univariate and multivariate analysis this not found to be significant.

Recurrence

6 patients (14%) recurred within a mean period of 20 months (range 2 to 50 months). Only 3 patients underwent redo metastasectomy and all three had a mean survival of 34 months (range 22 to 50 months) and only one expired , however all patients who did not undergo metastasectomy expired within a mean period of 4 months.

Prognostic grouping

A prognostic group was made based on number of metastases and DFI. They were considerd low risk Group I – Resectable , no risk factors (DFI > 36 months and single metastases), intermediate risk , Group II (DFI < 36 months or multiple metastases) , and high risk, Group III (DFI <36 months and multiple metastases). In patients who where in Group III

the survival was 65% at 36 months , in Group II there was 75% survival at 36 months and 50 % at 60 months respectively , and in patients with Group I the survival of 88% at 36 months. This was also not found to be significant in both univariate and multivariate analysis.

Post operative mortality and complications

There was no 30 day post operative mortality and only 6% morbidity (3 patients, 2 were cardiac events in the form of SVT, and the other was pulmonary which required postoperative mechanical ventilation).

DISCUSSION

The benefit of pulmonary metastasectomy is still questioned by physicians because patients are offered this treatment to a highly select group of patients and on a highly individualized basis depending on the philosophy and policy of the treating physician and the institute. The prognosis of these patients without surgical resection is still fully not known and its unlikely that the benefit of surgical resection compared with supportive care alone could alone be defined in randomized manner prospectively. Marcove et al documented that the natural history of unresected pulmonary metastasis was associated with 50% mortality at 1 year, 88% mortality at 2 years,95% at 3 years and none survived 5 years [40]. With improved medical and surgical treatments it has been possible now to attain a 5 year survival of 50% [41].

In this study the overall survival in the entire cohort of patients was 66% at 5 years which is higher than seen in the literature (34% at 5 years) because of the selection bias and small number of patients [42]. There was a tendency to offer metastasectomy to patients who had

longer disease free interval as can be seen in our frequency of DFI where almost 74% of patients had DFI of greater than 12 months and among them majority had DFI of greater than 36 months (41%). Other problem in this study was about 30 % of the patients were to lost to follow up after an average time of 32 months (range 19 to 60 months) , hence information on events beyond this was unavailable so as to give a meaningful survival figures at 5 years. Though the variables like decreasing DFI , increase in no of metastasis, increase in size of lesion, R1 resections, bilateral presentation and mediastinal lymphnode positivity were associated with decreased survival at 3 years ,these were not found to be significant in univariate or multivariate analysis using Cox regression analysis.

Epithelial tumours had lower survival at 3 years in comparison with sarcomatous tumours which is also in occurrence with the literature[41]. Patients with osteosarcoma had longer survival than soft tissue sarcoma at 36 months after metastasectomy (76% and 72% respectively). The reasons may be multifactorial, like chemotherapy offered for patients who had synchronous metastases, and probably because of the inherent natural history of the lesion developing after a

long DFI. Also it is a fact that synchronous metastases in osteosarcoma need not represent a more aggressive disease, which is however not true in patients with epithelial cancer.

Our attempt to identify a good prognostic group based on the risk factors like completely resected lesions, DFI and number of metastases was not successful as it failed to show significance in univariate and multivariate analysis, though there was difference in survival between good risk and poor risk groups (88% and 65% at 36 months).

Another observation in this study was in patients who recurred after metastasectomy and could undergo a R0 redo metastasectomy, had an average survival of 34 months (22 to 50 months) in comparison to patients who could not undergo metastasectomy as none of them survived beyond 7 months (mean of 4 months). This was also observed in the International Registry of Lung Metastasis study [41]. This good survival observed in patients who underwent redo metastasectomy can be explained by the inherent biology of the lesion as these patients had an average time to recurrence of 22 months (15 to 41 months)

However in spite of all these shortcomings it can be confirmed that metastasectomy is a potentially curative treatment that can be done safely with low mortality or morbidity. In our series there was no 30 day post operative mortality and only 6% morbidity (3 patients, 2 were cardiac events in the form of SVT, and the other was pulmonary which required postoperative mechanical ventilation).

CONCLUSIONS

1. Pulmonary metastasectomy is a potentially curative treatment that can be done safely with low mortality or morbidity.
2. Good prognostic variables like increasing DFI (> 1 year), ability to do R0 resection, solitary metastasis, size of the lesion less than 1 cm, and absence of mediastinal nodal positivity showed a trend towards improved survival. Good prognostic group selected on the basis of the risk factors like completely resected lesions, DFI and number of metastases show a difference in survival between good risk and poor risk groups (88% and 65% at 36 months). Although these were not found to be significant in univariate or multivariate analysis using Cox regression analysis.
3. There is a need for larger multicenteric analysis of data with larger duration of follow up, from specialized centres who practice pulmonary metastasectomy, to arrive at definite conclusions.

REFERENCES

1. Barney JD, Churchill EJ: Adenocarcinoma of the kidney with metastasis to the lung: Cured by nephrectomy and lobectomy. J Urol 42:269, 1961.

2. Barney JD: Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. J Urol 52:406–407, 1944.

3. Divis G: Ein Beitrag Zur Operativen Behandlung der Lungeschwulste. Acta Chir Scand 62:329–341, 1927.

4. Edwards AT: Malignant disease of the lung. J Thorac Surg 4, 107–124, 1934.

5. Alexander J, Haigh C: Pulmonary resection for solitary metastatic sarcomas and carcinomas. Surg Gynecol Obstet 85:129–146, 1947

6. Liotta LA: Cancer metastasis and angiogenesis: An imbalance of positive and negative regulation. Cell 64:327–336, 1991

7. Liotta LA, et al: The significance of hematogenous tumor cell clumps in the metastatic process. Cancer Res 36:889–894, 1976.

8. Fidler IJ: Molecular biology of cancer: Invasion and metastasis. In De Vita V, Hellman S, Rosenberg SA, editors: Principles and Practice of Oncology

9. Pass HI, Donington JS: Metastatic cancer of the lung. In De Vita V, Hellman S, Rosenberg SA, editors: Principles and Practice of Oncology. Philadelphia: J.B. Lippincott, 1997, pp. 2536–2551.

10. Cahan W, Castro E, et al: Benign solitary lesions in patients with cancer. Ann Surg 187:241–249, 1978

11. Crow J, Slavin G, Kreel L: Pulmonary metastasis: A pathologic and radiologic study. Cancer 47:2595–2601, 1981.

12. Steele JD: The solitary pulmonary nodule. J Thorac Cardiovasc Surg 46:21–36, 1963.

13. Feuerstein IM, Jicha DL, Pass HI, et al: Pulmonary metastases: MRI imaging with surgical correlation—A prospective study. Radiology 182:123–129, 1992.

14. Strauss LG, Conti PS: The applications of PET in clinical oncology. J Nucl Med 32:633–648, 1991.

15. Beattie EJ Jr, Matini N, Rosen G: The management of pulmonary metastases in children with osteogenic sarcoma with surgical resection combined with chemotherapy. Cancer 35: 618–621, 1975

16. Rosen G, Suwansirikul S, Kwon C, et al: High-dose methotrexate with citrovorum factor rescue and adreamycin in childhood osteogenic sarcoma. Cancer 33:1151–1163, 1974.

17. Skinner K, Eilber F, Holmes E, et al: Surgical treatment and chemotherapy for pulmonary metastases from osteosarcoma. Arch Surg 127:1065–1071, 1992.

18. Putnam JB Jr, Roth JA, Wesley MN, et al: Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas. J Thorac Cardiovasc Surg 87:260–267, 1984.

19. Pastorino U, McCormack PM, Ginsberg RJ: A new staging proposal for pulmonary metastases: The results of analysis of 5206 cases of resected pulmonary metastases. Chest Surg Clin North Am 8:197–202, 1998.

20. Temple LK, Brennan MF: The role of pulmonary metastasectomy in soft tissue sarcoma. Sem Thorac Cardiovasc Surg 14(1):35–44, 2002.

21. Weiser MR, Downey RJ, Leung DH, et al: Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. J Am Coll Surg 191(2):184–190, 2000.

22. McCormack PM, Burt ME, Bains MS, et al: Lung resection for colorectal metastases. 10 years results. Arch Surg 127: 1403–1406, 1992

23. Schulten MF, Heiskell CA, Shields TW: The incidence of solitary pulmonary metastasis from carcinoma of the large intestine. Surg Gynecol Obstet 143:727–729, 1976.

24. Yamada H, Katoh H, Kondo S, et al: Surgical treatment of pulmonary recurrence after hepatectomy for colorectal liver metastases. Hepato-Gastroenterology 49(46):976–979, 2002.

25. Sakamoto T, Tsubota N, Iwanaga K, et al: Pulmonary resection for metastases from colorectal cancer. Chest 119(4):1069–1072, 2001.

26. Casey JJ, Stempel BG, Scanlon EF, Fry WA: The solitary pulmonary nodule in the patient with breast cancer. Surgery 96: 801–805, 1984.

27. Raab SS, Berg LC, Swanson PE, et al: Adenocarcinoma in the lung in patients with breast cancer: A prospective analysis of the discriminatory value of immunohistology. Am J Clin Pathol 100:27–35, 1993.

28. Simpson R, Kennedy C, Carmalt H, et al: Pulmonary resection for metastatic breast cancer. Austr New Zeal J Surg 67(10):717–719, 1997.

29. Xiao H, Liu D, Bajorin D, et al: Medical and surgical management of pulmonary metastases from germ cell tumors. Chest Surg Clin North Am 8:131–143, 1998.

30. Tafra L, Dale PS, Wanek LA, et al: Resection and adjuvant immunotherapy for melanoma metastatic to the lung and thorax. J Thorac Cardiovasc Surg 110:119–124, 1995.

31. Harpole DH, Johnson CM, Wolfe WG, et al: Analysis of 945 cases of pulmonary metastatic melanoma. J Thorac Cardiovasc Surg 103:743–750, 1995.

32. Ollila DW, Morton DL: Surgical resection as the treatment of choice for melanoma metastatic to the lung. Chest Surg Clin North Am 8:183–196, 1998.

33. Leo F, Cagini L, Rocmans P, et al: Lung metastases from melanoma: When is surgical treatment warranted?. Br J Cancer 83(5):569–572, 2000.

34. Liu D, Labow DM, Dang N, et al: Pulmonary metastasectomy for head and neck cancers. Ann Surg Oncol 6(6): 572–578, 1999.

35. Piltz S, Meimarakis G, Wichmann MW, et al: Long-term results after pulmonary resection of renal cell carcinoma metastases. Ann Thorac Surg 73(4):1082–1087, 2002.

36. Friedel G, Hurtgen M, Penzenstadler M, et al: Resection of pulmonary metastases from renal cell carcinoma. Anticancer Res 19(2C):1593–1596, 1999.

37. Khan JH, McElhinney DB, Rahman SB, et al: Pulmonary metastases of endocrine origin: The role of surgery. Chest 114(2):526–534, 1998.

38. Seki M, et al: Surgical treatment of pulmonary metastases from uterine cervical cancer. Operation method by lung tumor size. J Thorac Cardiovasc Surg 104:876–881, 1992.

39. Jones WB, Romain K, Erlandson RA, et al: Thoracotomy in the management of gestational choriocarcinoma. A clinicopathologic study. Cancer 72(7):2175–2181, 1993.

40. Burt ME, Liu D, Abolhoda A, et al: Isolated lung perfusion for patients with unresectable metastases from sarcoma: A phase I trial. Ann Thorac Surg 69(5):1542–1549, 2000.

41. Marcove R, Martini N, Rosen G. The treatment of pulmonary metastasis in osteogenic sarcoma. Clin Orthop 1975;111:65.

42. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37.

43. Saeter G, Hoie J, Stenwig AE, et al. Systemic relapse of patients with osteogenic sarcoma. Prognostic factors for long term survival. Cancer 1995;75:1084.

44. Meyers PA, Heller G, Healey JH, et al. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol 1993;11:449.

PROFORMA

Name	Complications
Age	Chemotherapy
Sex	Preop
Type	Adjuvant
DFI	Recurrence
Approach	Months for recurrence
Resection	Site of Recurrence
No.of Mets	Redo Metastasectomy
Size	Recurrence after Redo
Completeness	Site of Recurrence (2)
Nodes	Months after Metastasectomy
Postop Stay	Follow Up Status